UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/051,159	01/13/99	BALMAIN A	CCI-005US

EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	15

HM22/0215

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DATE MAILED: 02/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/051,159	Applicant(s) Balamain
	Examiner Peter Brunovskis	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-24 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-24 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7, 8

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The declaration has not been signed by co-inventor Jingde Zhu. Acknowledgment is made of the letter from Jingde Zhu, filed 9/15/2000 (Paper No. 13) to the PCT Legal Office expressing co-inventor Zhu's desire to be involved with the prosecution of the application.

Claim Objections

The preliminary amendment, filed 1/13/98 is objected to, because the amendment is not in accordance with 37 CFR 1.121(a)(2)(ii) which states:

> (ii) Claim cancellation or rewriting: A claim may be amended by directions to cancel the claim or by rewriting such claim with underlining below the matter added and brackets around the matter deleted. The rewriting of a claim in this form will be construed as directing the deletion of the previous version of that claim. If a previously rewritten claim is again rewritten, underlining and bracketing will be applied relative to the previous version of the claim, with the parenthetical expression "twice amended," "three times amended," etc., following the original claim number. The original claim number followed by that parenthetical expression must be used for the rewritten claim. No interlineations or deletions of any prior amendment may appear in the currently submitted version of the claim. A claim canceled by amendment (not deleted and rewritten) can be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number.

Claim 1 is objected to because it lists a number of changes relative to the originally filed claims that are not properly rewritten using appropriate bracketing. Thus, it is unclear whether claims 1-7, 10, 13, 15, 18, 19, 21, and 23, not listed in the preliminary amendment as "(Reiterated)", also carry additional changes, in addition to the claims listed as "(Amended)". Consequently, these claims will not be entered; for purposes of examination, claims 1-7, 10, 13, 15, 18, 19, 21, and 23 will be examined in accordance with the claims as originally filed in the 35 U.S.C. 371 application.

Claims 1-19, 21, 23, and 24 are objected to because of the following informalities:

In claim 1, line 3 (of the originally filed claim, p. 71), the period between "controlled" and "by" should be removed.

In dependent claims 2-21, 23, and 24, "A" (as in "A composition according to...") should be changed to --The-- (e.g. --The composition according to...--).

In claim 10, line 1, "a" in "a said nucleic acid vector" should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) is very unclear; the recitation presented does not allow for a clear or accurate rendering of its metes and bounds. As presently written, it is unclear whether there exists any promoter which meets the limitations of the claim or whether all promoters (except for constitutive promoters) meet the recited claim limitations. The claim recites a promoter "whose function is suppressed in non-tumour cells" and another promoter "that is up-regulated in non-tumor cells". However, the metes and bounds of these phrases are unclear, since these phrases are not clearly defined in the specification. For example, it is unclear whether the "suppress[ion]" or up-regulation of the first and second promoter, respectively, is a characteristic of the natural promoter or is due to e.g. the first promoter being down-regulated when the second gene, the sequence-specific transcriptional suppressor, is present. Further, the claim appears to suggest that the first promoter is always suppressed in non-tumor cells, while the second promoter is always up-regulated in non-tumor cells. However, any regulated promoter is capable of being suppressed or "up-regulated" depending on the actions of stimuli (e.g. phosphorylation, transcription factor availability, protein-protein interactions etc.). Thus, essentially any regulated promoter can meet or fail to meet the recited limitations at one time or another. It is essentially impossible to determine the metes and bounds of the claim as written, because of the indefiniteness of these phrases and because there is no context for knowing how to apply

"suppressed" or "up-regulated" within the limited context of a "non-tumour cell"; use of the terms "suppressed" and "up-regulated" in relation to promoters is highly context-specific and dependent on specific factors or stimuli which are not recited in the claim (e.g. p53).

Additionally, the claim is indefinite since it recites a composition, which at a minimum, contains a first nucleic acid construct and a second nucleic acid construct; however, there is no clear structural nexus between these constructs and any of the genes or promoters recited. The claim merely states that the genes are part of the composition, and *may be expressed from the nucleic acid constructs* such that they are either "controlled by a first promoter whose function..." or are "controlled by a second promoter that is up-regulated in non-tumor cells". However, the claims do not recite whether the genes or promoters are actually on the nucleic acid constructs, whether the promoters are operatively linked to the genes, or whether they merely represent the promoters that typically control expression of those particular genes in their native context. The compositions should be recited in accordance with structural limitations, as opposed to process steps, which further renders indefinite the metes and bounds of the claim.

Claims 2-4 are indefinite in their recitation of compositions defined by process steps in accordance with claim 1. Changing the claims in accordance with structural limitations would obviate the problem. For example, changing claim 4 to:

--The composition of claim 1 wherein said second gene of said second nucleic acid construct encodes a sequence-specific transcriptional suppressor and said first nucleic acid

construct comprises a binding site recognized by said sequence-specific transcriptional suppressor--

would obviate the problem in regard to claim 4.

Claims 6 and 7 are indefinite in their recitation of the term "suppression domain" since it is unclear how this term is defined, what it is directed to, or what its metes and bounds are. Changing the term to --transcriptional suppression domain-- would appear to obviate the problem.

Claim 9 (and dependent claims) recites the limitation "the same nucleic acid vector" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Amending the phrase to --a single nucleic acid vector-- would obviate the problem.

Claim 12 is indefinite in recitation of the phrase "CMB promoter" since it is unclear what the abbreviation "CMB" is directed to or how it is defined.

Claims 12 and 13 are indefinite because it is unclear what the structural relationship is between the second nucleic acid construct and the limitations that follow. For example, it is unclear in claim 12 how the phrase "*includes* a p53 binding site sequence or CMB promoter" (emphasis added) further limits its base claim. Specifically, it is unclear whether the nucleic acid construct comprises the p53 binding site sequence or CMB promoter *in addition* to the second promoter of the second nucleic acid construct or whether these limitations are intended to further limit the second *promoter*. Further, in claim 13 it is unclear whether the p53 binding site sequence is downstream of the TATA Box only, or whether it is downstream of both the TATA box and the transcriptional start site. Since the structural relationship between the nucleic acid construct

and the sequence(s) or promoter(s) which follow are unclear, it is difficult to evaluate what functional role is conferred by these elements for purposes of utility or enablement. Changing e.g. claim 12 to --wherein said second promoter comprises a p53 binding site or CMB promoter-- would appear to obviate the problem.

Claim 17 is indefinite in its recitation of the term "antitumour agent" since it is unclear how this term is defined or what its meets and bounds are.

Claims 20 and 21 are indefinite in their recitation of "[a] cell containing..." (cl. 20) or "[a] cell according to..." (cl. 21), since it is unclear what metes and bounds apply to said claim. For example, it is not clear whether the claims are drawn to an isolated cell and/or whether they embrace a cell within e.g. a body.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, and 20-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The subject invention is described as "relat[ing] to the control of proliferation of tumour cells, preferably by killing those cells" (p. 1, lines 1-3) and as "[m]ore particularly...relat[ing] to

methods and means for selectively attacking tumour cells with cytotoxic or antiproliferative agents" (lines 3-5). Further, the invention is described as allowing for "selectivity for expression of the tumour agent...by a combination of two approaches: (i) up-regulation of the mediating gene in tumor cells and (ii) down-regulation of the mediating gene in normal cells" (p. 3, lines 16-21). "A preferred basis for [the] approach is centred around the p53 gene" (p. 3, lines 26-27) by "exploit[ing] differences in the transcriptional activation and stability functions of the p53 protein between normal and tumour cells" (p. 4, lines 16-18) by utilizing a first genetic unit wherein "the antitumour gene is controlled by a promoter whose function is suppressed by wtp53, but is not suppressed by mutant p53" (p. 4, lines 25-27) and a second genetic unit wherein "a gene for down-regulating the antitumour gene in normal cells is controlled by a promoter containing the p53 binding site, and which is therefore potently up-regulated by wtp53 but not by mp53, [such that] the wtp53 in normal cells is used to up-regulate a gene which downregulates the expression of the antitumour agent in those normal cells" (p. 4, line 28 through p. 5, line 7). Most of the specification provides a description of the design and development of *this specific "p53-centred" system*, including the use of down-regulating genes in different "forms" (e.g. antisense, ribozyme, sequence-specific transcriptional suppressors).

The specification further characterizes the invention as "preferably based on the p53 gene, because of its central role in tumour suppression and the differences in its function in normal and tumour cells...[but further states that]...the general concept of the invention may be applicable using other genes to up-regulate the antitumour agent in tumour cells and to down-regulate it in

normal cells...[and that]...since the natural tumour suppressor pathways are complex and involve many genes, at least some of them could be used in a similar fashion" (paragraph abridging pp. 5-6). However, apart from p53, the only other gene described in the specification "as being associated with the tumour suppression pathway [that] may be utilised in the present invention...[is]...the p16 INK4A gene" (p. 12, lines 2-4), for which the p16 promoter is reasoned as being likely (i.e. "should therefore be") to be strongly up-regulated in Rb-negative tumours, and could be used as the type I promoter in our dual construct" (lines 9-12).

The rejected claims lack adequate written description primarily because the specification only discloses compositions comprising use of a first p53-responsive promoter down-regulated in non-tumour cells, but up-regulated in tumor cells carrying mutant p53, and further comprising a second wild-type p53-responsive promoter operatively linked to an effector product that down-regulates the first promoter in non-tumour cells. However, when viewed in light of claim 14, claim 1 (and depending claims) appear to embrace embodiments comprising a first promoter down-regulated in non-tumour cells *without any further requirements concerning its ability to be up-regulated in tumor cells*. The specification provides insufficient written description of any such embodiments.

The rejected claims embrace a broad range of promoters whose function is either: "suppressed in non-tumor cells" (cl. 1); "up-regulated in non-tumor cells" (cl. 1); and/or "up-regulated in tumor cells" (cl. 14). However, the specification provides a limited description of promoters that meet these limitations; importantly, the only promoters adequately described in the

instant specification are those whose function is *suppressed in non-tumor cells, but up-regulated in tumor cells in accordance with a particular p53 status*. Further, it should be noted that use of the terms "up-regulated"- or "down-regulated promoter[s]" is only meaningful within the context of a *specific* active stimulus or factor that can exert this pattern of regulation. The specification only describes a limited number of promoters appropriate for a "Type I genetic unit", positively responsive to cells carrying a mutant p53 or null 53 phenotype and negatively responsive to normal wtp53-positive cells (e.g. HSP70, MDR1, PCNA, p. 10; and certain modified HSP70 promoters variants carrying inserted lacO-, tetO- or Gal-4 binding sites, e.g. pp. 35-37). The only other candidate "Type I" promoter for use with the claimed method not directly linked to the mutant p53 "gain of function" pathway is the p16 INK4A promoter.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification provides a written description for various specific promoters responsive to wtp53, mutant p53, or to the absence of p53 (e.g. HSP70, MDR1, and PCNA), the specification fails to describe the other genuses of promoters up-regulated or down-regulated in tumour and/or non-tumour cells as recited in the claims with particularity to indicate that

applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case the claimed promoter-containing compositions and methods for administering such lack a written description. The specification fails to describe what promoters and their effectors fall into these genuses and it was unknown as of applicants effective filing date that any promoters other than those explicitly described would have the properties of "up-regulation" or "down-regulation" within the context of tumor and/or non-tumor cells. The skilled artisan cannot envision the detailed chemical structure of the promoters or their effectors, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method for identifying or isolating such. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only those specific promoters positively responsive to mutant or no p53 and negatively responsive to wild-type p53 of normal cells as described in the instant specification meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In view of the difficulties in interpreting the metes and bounds of claim 1 (and dependent claims) as set forth in the 112 2nd paragraph indefiniteness rejection above, it is not clear whether Applicants have taught how to make or use any embodiments that meet the recited claim limitations, since it is unclear whether e.g. the "suppression" or "up-regulation" is an absolute property characteristic of the promoter itself, independent of anything else, or whether these limitations merely recite properties that *can be* observed under certain conditions. Regardless, the specification can only be enabled for compositions and methods of using to the extent they have

been described. As noted in the written description rejection above, the specification only discloses compositions comprising use of a first promoter down-regulated in non-tumour cells through the action of wild-type p53, but up-regulated in tumor cells by mutant p53, wherein a second wild-type p53-responsive promoter operatively linked to an effector product is included to down-regulate "leaky expression" from the first promoter in non-tumour cells. Apart from those embodiments specifically disclosed in the specification for use in up-regulating antitumour agents in tumor cells, while down-regulating those same agents in normal cells through a p53 pathway (i.e. using either HSP70-, MDR1-, PCNA promoters or variants thereof), the specification fails to provide sufficient guidance teaching how to make or use any other compositions for use in a non-p53 based method or in accordance with the composition of claim 1, wherein the first promoter is only suppressed in non-tumor cells (i.e. not up-regulated in tumor cells also). However, even for those enabled embodiments that are disclosed in the specification, it is not clear how e.g. a TK or CMV "second promoter" in a "Type II unit" would be considered to meet the limitations of being "up-regulated" in non-tumour cells. Furthermore, except for HSP70-, MDR-1, and PCNA promoters, the specification fails to disclose any other promoters that specifically down-regulated in non-tumor cells, but up-regulated in tumor cells. However, this difference is only observed in the context of certain mutant p53-containing cells exhibiting a "gain of function" phenotype; the specification does not teach how to make or use any other promoters for either mutant p53-cell-specific expression or any other non-mutant p53-mediated pattern of expression having a patentable utility. Although the specification *suggests the possibility* of using a p16INK4A

promoter as a Type I promoter for treating Rb-negative tumors; the specification merely suggests that in view of the high p16 levels in Rb negative tumours, "the p16 promoter *should* therefore be strongly up-regulated" (emphasis added, p. 12, lines 9-11). Absent evidence to the contrary, there is no evidence of record indicating a positive correlation between high p16 levels observed in Rb-negative tumours and a higher promoter inducibility in such cells to support the use of this promoter in the suggested method.

In spite of the assertion in the specification that "the general concept of the invention may be applicable using other genes to up-regulate the antitumour agent in tumour cells and to down-regulate it in normal cells" (top paragraph, p. 6), the specification fails in its burden to provide sufficient guidance on how to identify other such genes or promoters commensurate with the scope with the claimed invention. Extrapolation of this "concept" to other as yet undeveloped promoters (i.e. p16INK4A) or other as yet undiscovered genes or promoters in accordance with the claimed invention falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

The specification admits that "the natural tumour suppressor pathways are complex and involve many genes...[and while asserting that]...at least some of them could be used in a similar fashion" (p. 6, lines 5-8), it provides insufficient guidance concerning the design or development of any other antitumour expression systems in accordance with the claimed method. In fact, the specification appears to suggest the *unlikelihood* of finding any other "single tissue-specific or tumour-selective gene promoter...[that would]...give sufficient discrimination between normal and tumour-cells...[and therefore]...propose the use of both altered transcriptional control by wild-type and mutant p53 and altered translation or stability of the p53 protein itself to control...expression...for the purpose of gene therapy" (p. 8, lines 2-10).

The claimed subject matter drawn to methods of *in vivo* administration of the nucleic acid constructs of the claimed invention (i.e. cl. 22-23) or cells comprising such *in vivo* (i.e. cl. 20-21). The specification does not present any substantial or well-established utility for the claimed in vivo methods or compositions apart from use in methods of gene therapy. For example, the specification does not present any practical utility or provide sufficient guidance for using the compositions or methods comprising anything other than a pro-drug activating enzyme (i.e. TK) in the "Type I unit" of the first nucleic acid construct to kill tumor cells in a body.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. This is not to say that gene delivery and

expression at a sub-therapeutic level was unpredictable at the time of filing. Blau et al stated that the main challenge in gene therapy is the achievement of efficient vector delivery and gene expression (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Crystal (1995) stated that human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy (abstract) and that the human transfers had been plagued with inconsistent results (page 409, col. 1, parag. 2, lines 1-4). Miller et al (1995) that before gene therapy is an option for treating genetic diseases, there is a requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells either in vivo or ex vivo accurately and efficiently (page 190, col. 1, parag. 1, lines 1-7).

Orkin et al. reviewed the infant state of the art of gene therapy at around the time the invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression

that gene therapy is successful is mistaken (pages 1-2). The specification does not teach how one skilled in the art is to overcome any of the problems that have plagued gene therapy.

Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Ross et al (1996) state that the technical impediment to gene transfer (as a therapy) is the lack of vector systems, and that unless it is possible to deliver the gene to the appropriate blood or body cells and in sufficient quantities, gene therapy will not be efficacious (page 1782, col. 2, parag. 1, lines 1-4).

In view of the unpredictability and lack of success in the art at the time of filing, gene therapy can only be considered predictable in being shown not to work. Thus to overcome these teachings in the art the specification would need to supply direct, correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective in alleviating symptoms of disease using the claimed expression system. Thus, the need for working examples in appropriate animal model studies is critical. However, apart from the vague outlines of a prophetic example (e.g. p. 59), the specification lacks the appropriate specific guidance referred to above that would be necessary to overcome the problems and the unpredictability in the art. Specifically, there are no teachings in the specification that would provide the artisan with any treatment regime to achieve a therapeutic benefit by in vivo or ex vivo gene therapy and provides no correlation between vectors, cells comprising vectors, routes of delivery (e.g. intratumoral, intravenous etc.), dosage amounts/frequencies, and specific tumors

treatable by the said of the instant specification. Such specific teachings are particularly necessary, since e.g. bystander-mediated killing as proposed in the instant specification (e.g. p. 2) was known at the time of filing as being dependent on the extent of heterocellular communication mediated by gap junctions (Fick et al., Proc. Natl. Acad. Sci. USA, 92:11071-11075, 11/95) whose effects are variable among different tumor cells (Beck et al., Hum. Gene Ther., 6:1525-1530, 12/95). Specifically, the specification provides no guidance concerning the specific types of tumors amenable to the bystander effect in accordance with the claimed invention, including routes of vector administration, ganciclovir dosages etc. For example, even though administration of a single vector comprising both nucleic acid constructs would be much more efficient for co-delivery of nucleic acid constructs compared to *co*-transfection (or administration) of two independent nucleic acid constructs, the specification does not disclose what amounts of vector and prodrug need to administered or co-administered (in either case) so as to allow sufficient discrimination between tumor and non-tumor cells to result in e.g. selective TK expression in tumor cells to produce a therapeutic benefit. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 4, 8, 12, 14, 16, and 20-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Deuschle et al., (Mol. Cell. Biol., 15(4):1907-1914, 4/95).

Deuschle discloses a composition including a first nucleic acid construct comprising luciferase reporter operatively-linked to a first promoter whose function is suppressed in non-tumour cells (e.g. ptetO7-CMV-L), and a second nucleic acid construct comprising a sequence-specific tetR-KRAB that downregulates expression of the luciferase reporter in non-tumour cells , wherein expression of the tetR-KRAB suppressor is up-regulated in non-tumour cells through its operative linkage to the CMV promoter. It is noted that ptetO7-CMV-L includes a binding site sequence (i.e. tetO) for the tetR-KRAB suppressor. Deuschle further anticipates claim 12 to the extent it reads on a second nucleic acid construct including a CMV (rather than CMB) promoter, since the tetR-KRAB construct includes a CMV promoter. Deuschle further discloses a method of introducing said constructs in a tumor cell (HeLa) in vitro. It is noted that the constructs disclosed by Deuschle would meet the limitations recited in e.g. cl. 1 independent of whether the cell is a tumor cell or a non-tumour cell, since the constructs only require CMV-mediated expression of tetR-KRAB to suppress the CMV-tetO-driven luciferase reporter gene.

Claims 1, 5, 8, 14, 16, 20-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Hannan et al., (Gene, 130:233-239, 1993).

Hannan discloses a composition including a first nucleic acid construct comprising luciferase reporter operatively-linked to a first promoter whose function is suppressed in non-tumour cells (e.g. pPN508; Fig. 2, p. 236), and a second nucleic acid construct (e.g. pPGKLacIN) comprising a sequence-specific lac suppressor that downregulates expression of a CAT reporter in non-tumour cells, wherein expression of the lac operator suppressor is up-regulated in non-tumour cells through its operative linkage to the PGK promoter (see e.g. Fig. 3, p. 237). Hannan further discloses a method of introducing said constructs in a tumor cell (African monkey CV1 cells) in vitro. It is noted that pPN508 includes a binding site sequence (i.e. lacO) for the lac suppressor. Hannan further discloses a method of introducing said constructs in a tumor cell (HeLa) in vitro. It is noted that the constructs disclosed by Hannan would meet the limitations recited in e.g. cl. 1 independent of whether the cell is a tumor cell or a non-tumour cell, since the constructs only require PGK-mediated expression of the lac operator suppressor to suppress the PGK-lacO-driven CAT reporter gene.

Claims 1-4, 8, 9, 11, 13, 14, and 16-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Bujard et al. (U.S. 6,004,941, filed 6/7/95).

Bujard discloses compositions including a first nucleic acid construct comprising a first promoter operatively linked to a coding region or active RNA molecule (col. 18, lines 37-43)

whose function is either down-regulated in non-tumour cells or up-regulated in tumour cells, and a second nucleic acid construct, on the same or different vector, including a viral vector (col. 12, lines 62-66), further comprising a sequence-specific transcriptional suppressor, comprising a transcriptional suppression (or silencer) domain (e.g. col. 26, line 66 through col. 28, line 48; Example 5, col. 51-52) that together serve to downregulate expression of the coding region or active RNA in tumour or non-tumour cells (col. 89, cl. 13), wherein expression of the sequence-specific suppressor is up-regulated in non-tumour cells through its operative linkage to a selected promoter. Bujard discloses binding site sequences (i.e. tetO) for the sequence-specific and prodrug activating enzyme genes, including thymidine kinase (col. 24, lines 29-33; col. 39, lines 59-62), for use in the first nucleic acid construct. Bujard further anticipates claim 12 to the extent it reads on a second nucleic acid construct including a CMV (rather than CMB) promoter (see e.g. Fig. 11). It is noted that the constructs disclosed by Bujard would meet the limitations recited in e.g. cl. 1 independent of whether the cell is a tumor cell or a non-tumour cell, since the constructs only require expression of the sequence-specific transcriptional suppressor to suppress the tetO-linked nucleic acid sequences.

Information Disclosure Statement

DE 195 02 584 A1 was only considered with respect to the English abstract, since no translation was supplied.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

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PRIMARY EXAMINER